2022-2217, 2023-1021

United States Court of Appeals for the Federal Circuit

UNITED THERAPEUTICS CORPORATION,

Plaintiff-Cross-Appellant,

– v. –

LIQUIDIA TECHNOLOGIES, INC.,

Defendant-Appellant.

On Appeal from the United States District Court for the District of Delaware in No. 1:20-cv-00755-RGA-JLH Honorable Richard G. Anders, Judge

CORRECTED DEFENDANT-APPELLANT'S RESPONSE AND REPLY BRIEF

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Abbreviation	Full Term
’066 patent	U.S. Patent No. 9,593,066
’393 patent	U.S. Patent No. 8,497,393
’793 patent	U.S. Patent No. 10,716,793
’793 FWD	Final Written Decision in IPR2021-00406
’901 patent	U.S. Patent No. 9,604,901
’901 FWD	Final Written Decision in IPR2020-007700
Asserted claims of the ’066 patent	Claims 1, 2, 3, 6, 8, 9
Asserted claims of the ’793 patent	Claims 1, 4, 6, 7, 8
Asserted Patents	’066, ’901, and ’793 patents
Board or PTAB	Patent Trial and Appeal Board
DMF	Drug Master File
cl.	claim
FDA	Food and Drug Administration
FIRST	Flolan International Randomized Survival Trial
FWD	Final Written Decision
GMP	Good Manufacturing Practice
IPR	*Inter partes* review
LHD	Left heart disease
Liquidia	Liquidia Technologies, Inc
Moriarty 2004	Moriarty et al., The Intramolecular Asymmetric Pauson−Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil), 69 J. Org. Chem. 1890 (2004)
NDA	New Drug Application
PAH	Pulmonary arterial hypertension (Group 1 PH)
PAP	Pulmonary arterial pressure
POP	Precedential Opinion Panel of the PTAB
PH	Pulmonary hypertension
POSA	Person of ordinary skill in the art

PRINT	Particle Replication in Nonwetting Templates
PVR	Pulmonary vascular resistance
TN	Treprostinil sodium
TRE or TN02	Treprostinil
UTC	United Therapeutics Corporation
WHO	World Health Organization
Yonsung	Yonsung Fine Chemicals

INTRODUCTION

"Treating pulmonary hypertension" in the '793 patent claims requires safely and effectively doing so. Otherwise, the claims encompass an alleged treatment that would increase the mortality rate of 50% of all PH patients covered by the claim. Thus, the district court erred in expressly excluding safety from the claim and UTC's inconsistent response only highlights this error. Because the court excluded safety from the "method of treating," it improperly found the claims enabled and adequately described based solely on hemodynamic changes that the experts, and even UTC on appeal, admit are not relevant for isolated Group 2 PH patients. Even if safety is excluded, POSAs would require undue experimentation to treat isolated Group 2 patients, and conclude the inventors were not in possession of the claimed invention because treprostinil is not effective in this patient population. For these reasons, the district court's decision should be reversed.

Additionally, there is no ambiguity in *Commil*: Liquidia is not liable for induced infringement of the '793 patent because it knows, via the PTAB's FWD, that the patent is invalid. UTC's purposeful disregard for the cited statutory provision—35 U.S.C. §316—and misdirection to uncited §318, underscores the lack of a legal basis to refute Liquidia's position. And the Supreme Court's decision not to cite §318 means that collateral estoppel is not required to negate liability upon an IPR finding of invalidity in a FWD issued 12-18 months after institution. For these

reasons, the court's finding that Liquidia is liable for induced infringement should be reversed.

Regarding UTC's cross-appeal, this Court should affirm the district court's decision finding product-by-process claims 1-3 and 6 of the '066 patent invalid. UTC cannot show legal error in the court's finding that Moriarty 2004 discloses the same product as the claims. The claimed "pharmaceutical composition comprising treprostinil" can be treprostinil free acid, and Moriarty 2004 discloses this same composition. UTC presents no evidence demonstrating a structural or functional difference between the two compositions, and instead relies on an irrelevant comparison of treprostinil ***free acid*** to treprostinil ***salt***. Further, the impurities-lowering limitation is a ***process*** step, and the claimed composition does not require any specific impurity or purity level. UTC also cannot show legal error in the court's finding of non-infringement of claims 6 and 8 because Yonsung's DMF and Liquidia's NDA ***require*** treprostinil sodium to be stored at 2º-8ºC, not at ambient temperature.

LIQUIDIA'S REPLY ARGUMENT

I. The District Court Erred in Concluding the Claims of the '793 Patent Are Enabled and Adequately Described

A. The District Court's Exclusion of "Safety" from the "Method of Treating Pulmonary Hypertension" Was Clearly Erroneous

Liquidia is not "attack[ing] a caricature" of the court's opinion. Red Br., 33. The district court said the "**claims do not require** '*safely and effectively* treating

pulmonary hypertension,'" and thus construed the claims to exclude "safety." Appx00063 (bold added); *see* Appx00065. Based on this construction, the court found the '793 claims enabled and adequately described. Appx0064-0065. UTC does not dispute that the court's construction means a patient's PH is "treated" if they experience a change in hemodynamics even if the patient dies due to the use of treprostinil. This simply cannot be correct. UTC's inconsistent response, asserting "there is no basis to insert the words 'safely and effectively' into the claims" (Red Br., 37), while simultaneously arguing the court's "interpretation" does cover using treprostinil "safely and effectively" (*id.* at 35), highlights the erroneous nature of the court's construction.

UTC incorrectly accuses Liquidia of "smuggl[ing]" a safety limitation post-trial. Red Br., 34-35. Liquidia consistently argued the claims require safety and effectiveness. In its pretrial brief, Liquidia stated "[t]he '793 patent lacks adequate written description of the [claimed] method of 'treating pulmonary hypertension[,]'" because it did not describe how the treatment was safe or overcame the risk of increased mortality for isolated Group 2 PH patients. Appx08845 (¶545); Appx08848 (¶554). In its pretrial briefing, UTC asserted the '793 patent allows for "maximized therapeutic benefits by ***safely*** delivering doses to the lungs" (Appx08647 (¶319)) and that "high doses of treprostinil could be delivered to a

patient … with ***fewer side effects***." Appx08648 (¶321).[1] At trial, Dr. Hill testified about the serious safety issues (increased mortality) when administering a prostacyclin like treprostinil to isolated Group 2 patients (Appx13171 (586:3-5); Appx13172 (587:23-588:5); Appx13173 (592:3-12); Appx13196 (681:12-682:1)), and Dr. Waxman (UTC's expert) confirmed he would not treat isolated Group 2 patients with a pulmonary vasodilator like treprostinil (Appx13190 (659:15-20); Appx13185 (637:8-12, 638:12-14); Appx13184 (633:24-634:2); Appx13191 (661:14-20, 662:21-25)).

UTC incorrectly contends the court included safety in its construction and is not "*excluded*" from consideration.[2] Red Br., 35, 36. The court's acknowledgment that POSAs may have "safety concerns" in treating isolated Group 2 PH patients with treprostinil does not alter its construction that the "**claims do not require** '*safely and effectively* treating pulmonary hypertension[.]'" Appx00063 (bold added). Safety was neither included nor considered by the court. UTC's acknowledgement that doctors "*always* consider" safety risks makes the district court's construction even more troubling. Red Br., 35-36.

[1] Bold/italics emphasis added throughout, unless otherwise noted.

[2] UTC makes this argument while also arguing that Liquidia is improperly importing a safety limitation into the claims. Red Br., 33-34, 36.

UTC also argues Liquidia's position would require a "heightened safety-and-efficacy limitation" "akin to what is required to obtain FDA approval," such that treprostinil becomes a "preferred" treatment option. Red Br., 32, 36-37, 39. Neither Liquidia nor Dr. Hill has advocated such a position. A "method of ***treating*** pulmonary hypertension" plainly requires doing so safely and effectively. Avoiding increased mortality due to "treatment" is not a "heightened" safety requirement—it is a baseline requirement for anything to be considered a "treatment" of a disease, recognized in the prior art. Appx29455-29465.

Finally, UTC asserts Liquidia's position is based on attorney argument that lacks specification support. Red Br., 37-39. The specification repeatedly touts the claimed invention's ability to safely treat PH. Blue Br., 25-26. UTC's contention that the specification cannot "operate to limit the claims beyond their own terms" (Red Br., 38), ignores "treating" in the claim. The trial record also establishes that "treating" requires doing so safely. Appx13171 (586:3-5); Appx13172 (587:23-588:5); Appx13173 (592:3-12); Appx13196 (681:12-682:1); Appx13190 (659:15-20); Appx13185 (637:8-12, 638:12-14); Appx13184 (633:24-634:2); Appx13191 (661:14-20, 662:21-25). POSAs stopped a clinical trial early because "an increased risk of death" was observed when a prostacyclin was administered to Group 2 PH patients. Appx29455, Appx29462. Liquidia is not seeking to "rewrite the claim," but instead to construe "treating pulmonary hypertension" consistently with the

specification and the understanding of POSAs, as supported by the experts and prior art.

B. The '793 Patent Claims Are Not Enabled[3]

Isolated Group 2 PH patients account for 50% of patients encompassed by the '793 patent claims.[4] Appx13167-13168 (568:9-569:5, 569:9-570:25, 571:2-573:1); Appx13172 (589:14-17); Appx30699-30710; Appx29500-29513; Blue Br., 9. Liquidia's non-enablement position is not, as UTC suggests, based on "a single embodiment," but instead a "substantial number" of patients the claims fail to enable.[5] Red Br., 44.

The district court found that treprostinil is a prostacyclin that will vasodilate the pulmonary vasculature and affect a patient's hemodynamics. Red Br., 39-40. But both experts agree, and UTC acknowledges, the underlying postcapillary cause of PH in isolated Group 2 patients is different from the other precapillary PH Groups such that a precapillary vasodilator like treprostinil would not be effective in this postcapillary population. Blue Br., 37-40; Red Br., 50-51. Given the differences

[3] UTC failed to address Liquidia's non-enablement argument if this Court were to construe "treating pulmonary hypertension" in accordance with its plain meaning to include safety. Blue Br., 24-28.

[4] UTC does not dispute this fact.

[5] Looking at PH delineated between ***pre***capillary and ***post***capillary PH, as UTC suggests (Red Br., 50-51), demonstrates isolated Group 2 is one of just two embodiments within the scope of the claim.

between isolated Group 2 PH patients and patients administered treprostinil in the '793 patent, UTC does not meaningfully dispute that treprostinil would not benefit Group 2 PH patients, and advocates excluding isolated Group 2 PH from the claims. Red Br., 49-51. Accordingly, undue experimentation is required to treat isolated Group 2 PH patients with treprostinil.

UTC incorrectly asserts that Liquidia "misapplies" the enablement standard by requiring treprostinil to be a "mainstay" or "preferred" treatment of isolated Group 2 PH. Red Br., 41. It is undisputed that treprostinil is ineffective in treating isolated Group 2 PH. Dr. Hill (Appx13172 (587:5-588:5); Appx13175 (600:2-9)), Dr. Waxman (Appx13185 (636:1-5)), and UTC (Red Br., 49-51) acknowledge this fact. The '793 patent lacks any guidance for a POSA to treat this patient population with treprostinil and, therefore, the specification ***has not*** made the full scope of "treating pulmonary hypertension" possible.[6] Appx00062-00063; Red Br., 42.

UTC distorts the record by claiming "there is no dispute that the claims are enabled for treating precapillary PH, which includes patients in all five PH groups."

[6] The Supreme Court's pending decision in *Amgen Inc. v. Sanofi*, No. 21-757, does not change the enablement analysis. Under any interpretation of the enablement law, the '793 patent is not enabled. The '793 patent does not teach the full scope of the claimed "method of treating [PH]" because it does not enable treating isolated Group 2 PH patients. Moreover, it does not teach a POSA how to make and use a method of treating isolated Group 2 PH patients with treprostinil without undue experimentation.

Red Br., 42. First, precapillary PH excludes 50% of the PH population, which have postcapillary PH (isolated Group 2). Second pre- and postcapillary ***combined*** PH patients, to which UTC refers, are not isolated Group 2 PH patients. *See* Appx13168 (571:1-573:1); Appx13183 (630:2-22). That the patent examples demonstrate treating Groups 1, 3, and 4 provides no guidance with respect to treating the remaining 50% of all PH patients within the claim—isolated Group 2. Third, Dr. Hill did not testify he used treprostinil to treat isolated Group 2 PH patients. Red Br., 42. Dr. Hill tried treprostinil in a pre- and postcapillary ***combined*** Group 2 PH patient (*i.e.*, not an isolated Group 2 PH patient), and even then, it was not successful. Appx13175 (599:9:14); Appx13176 (605:8-20).

With no specification disclosure for treating any Group 2 PH patient, UTC merely repeats the district court's finding regarding the general hemodynamic effects of treprostinil and the understanding that method of treatment claims do not require FDA approval. Red Br., 42-43 The district court's factual findings are, however, clearly erroneous.[7] Despite the FIRST study showing hemodynamic changes in isolated Group 2 PH patients taking epoprostenol, Dr. Waxman testified "any pulmonary vasodilator [including treprostinil] would probably not be needed"

[7] Pages 49-51 of UTC's Response Brief noting the inability of treprostinil to "treat" isolated Group 2 PH patients further support the clearly erroneous nature of the district court's factual findings regarding enablement. Red Br., 49-51.

for isolated Group 2 (Appx13185 (637:11-12)), and "[w]e wouldn't treat a patient whose [PVR] was normal [with pulmonary vasodilators] and in the isolated [Group 2 PH] disease state, the [PVR] is normal." Appx13191 (661:14-20, 662:21-25). And as Dr. Hill testified, the hemodynamic changes observed in Group 2 PH patients in the FIRST study were not beneficial. Appx13171 (585:4:14). Critically, despite an "acute hemodynamic improvement" (Red Br., 42), the FIRST study was stopped because it led to increased risk of death. Appx00064; Appx29455, Appx29461-29463. This ***failed*** study, relied upon by the court, does not support the enablement of the '793 claims. Appx00063-64.

Finally, UTC argues a POSA could simply "carve out" inoperative embodiments. Red Br., 43-45. This "embodiment"—isolated Group 2 PH—accounts for 50% of all patients (one of two embodiments) encompassed by the claims, and simply cannot be carved out to preserve validity.[8] *E.g.*, Appx13167-13168 (568:9-569:5, 569:9-570:25, 571:2-573:1); *Alcon Rsch., Ltd. v. Apotex, Inc.*,

[8] UTC half-heartedly distinguishes *Trustees of Boston University v. Everlight Electronics Co.*, 896 F.3d 1357 (Fed. Cir. 2018) by arguing that one of the embodiments there was impossible, whereas here it is not. Red Br., 45. That was not the deciding factor. As this Court explained, "[t]he inquiry is not whether it was, or is, possible to make the full scope of the claimed device … the inquiry is whether the patent's specification taught one of skill in the art how to make such a device without undue experimentation[.]" 896 F.3d at 1363. Undue experimentation, not impossibility as UTC suggests, was the crux of the *Trustees of Boston University* decision. *Id.* at 1363-64.

687 F.3d 1362, 1368 (Fed. Cir. 2012) ("Courts do not rewrite the claims to narrow them for the patentee to cover only the valid portion.").[9] Further, Dr. Hill's undue experimentation testimony was not merely that testing would be "difficult" or "complicated." Red Br., 44-45. Instead, he testified a POSA must undertake undue experimentation to determine if administering treprostinil to an isolated Group 2 PH patient was even feasible or safe in the first instance. Appx13170 (581:6-12); Appx13174 (595:13-20). The '793 patent provides no guidance suggesting an avenue of avoiding these life-threatening issues when administering treprostinil to isolated Group 2 PH patients. Appx13170 (579:25-580:23); Appx13172-13173 (590:25-591:10, 591:16-592:2); Appx13184 (634:22-635:13). There is also nothing in the literature instructing the use of treprostinil, or any prostacyclin, in isolated Group 2 PH while avoiding increased mortality. Appx13173 (593:2-18). One could not simply "repeat[]" the FIRST study (Red Br., 44) because of the increased mortality leading to study termination. Appx13173 (592:13-593:18). Based on this lack of guidance, Dr. Hill testified a POSA would need to "start at square one." *Id.* Disregarding this evidence and instead relying on hemodynamic changes alone,

[9] *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569 (Fed. Cir. 1984) is distinguishable because, there, the Court found that it "has ***not*** been shown to be [a] case" where "the number of inoperative combinations becomes significant," whereas here 50% (or one of two embodiments) are not enabled. *Id.* at 1576-77; Red Br., 44.

which the parties and experts agree is irrelevant to "treating" isolated Group 2 PH patients, was clearly erroneous. Thus, the '793 patent is not enabled.

C. The '793 Patent Claims Lack Written Description[10]

Despite claiming a method of treating "pulmonary hypertension"—which properly construed includes all five PH Groups—the patent never describes treating ***any*** Group 2 PH patient. Blue Br., 41-42.

UTC does not and cannot refute this lack of disclosure. UTC's expert confirmed the '793 patent specification never describes treating Group 2 PH. Appx13184 (634:22-635:13). Instead, to argue the '793 patent inventors had possession of the full claim scope including treatment of Group 2 PH patients, UTC relies on disclosures describing treprostinil administration to ***non-Group 2 PH*** patients and "hemodynamic effectiveness" of treprostinil in ***non-Group 2 PH*** patients. Red Br., 46-47. This is insufficient, particularly when both experts agreed that hemodynamic changes are not relevant to treating isolated Group 2 patients. Blue Br., 37-38 (citing Appx13172 (590:2-10), Appx13175 (599:9-14), Appx13191 (661:14-20, 662:21-25), Appx13185 (637:8-12, 638:12-14), Appx13184 (633:24-634:2)); *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1346 (Fed.

[10] Like enablement, UTC does not address written description if "treating pulmonary hypertension" is construed to require safely doing so because UTC's position rests on safety and effectiveness "not" being "a claimed result." Red Br., 48.

Cir. 2005) ("[A] patentee cannot always satisfy the requirements of section 112, in supporting expansive claim language, merely by clearly describing one embodiment of the thing claimed.").

UTC's assertion that written description does not "require[] disclosing a method of treatment that a physician would prefer or choose" is a red herring. Red Br., 47. Neither Liquidia, nor either party's expert, took this position. The relevant question is whether the specification sufficiently discloses treating Group 2 PH at all, such that a POSA would understand the inventors were in possession of the claimed invention. Blue Br., 40-41. Both experts agreed that it does not. UTC recognizes Group 2 PH has a different postcapillary cause—ventricle stiffening in the left heart—from other PH Groups. Red Br., 50. The specification's disclosure of treating non-Group 2 PH patients with treprostinil does not show that the inventors possessed a method of treating isolated Group 2 PH, as UTC's expert acknowledged. *See e.g.*, Appx13184-13185 (635:21-636:5) ("Do you recall Dr. Hill's testimony that a POSA would not have understood the inventors were in possession of a method of treating [PH] for at least isolated [Group 2 PH] patients? … Do you agree with his opinion? Well, I would agree that in purely isolated postcapillary disease [isolated Group 2], yeah, we would not consider any pulmonary vasodilator"); *see also* Appx13191 (661:14-20, 662:21-25). The district court improperly ignored this testimony.

UTC dismisses Liquidia's reliance on this Court's rulings in *Biogen* and *Nuvo* because those cases only require written description for "a *claimed* result." Red Br., 48. But treating isolated Group 2 PH patients ***is*** a claimed result. *See Nuvo Pharms. (Ireland) Designated Activity Co. v. Dr. Reddy's Lab'ys Inc.*, 923 F.3d 1368, 1384 (Fed. Cir. 2019) ("When the inventor expressly claims that result, our case law provides that that result must be supported by adequate disclosure in the specification."). Even assuming (incorrectly) that the claims do not require ***any*** safety, the specification does not describe hemodynamic changes in any Group 2 PH patient or that those changes constitute effective treatment of Group 2 PH. Liquidia's expert did not agree that the general disclosures about treprostinil effectiveness in non-Group 2 PH patients says anything about Group 2 PH patients.[11] Red Br., 47. Accordingly, the '793 patent does not adequately describe the full scope of the claimed invention and the district court's decision otherwise was clearly erroneous and should be reversed.

[11] UTC cites to trial testimony from Dr. Hill agreeing that "in the average patient, a single administration of Treprostinil … results in a beneficial reduction of pulmonary arterial pressure and/or vascular resistance." Red Br., 47. But Dr. Hill had already explained that the '793 patent only describes treating non-Group 2 PH patients (*see* Blue Br., 41) and that there would be no beneficial reduction of pressure or resistance in isolated Group 2 PH patients. Appx13171 (585:4-14). UTC's expert agreed. Appx13191 (661:14-20, 662:21-25).

D. The ’793 Patent Claims Are Not Limited to Precapillary PH

UTC alternatively argues the claims should be limited to treating precapillary PH, excluding isolated Group 2 PH (postcapillary PH). Red Br., 49-51. The district court found the plain meaning of “pulmonary hypertension,” supported by the specification, encompasses all five PH Groups, and is not limited to precapillary PH. Appx00059-00060. Both Drs. Hill and Waxman agreed. Appx13169 (575:22-576:25); Appx13170 (580:24-581:2); Appx13190-13191 (659:21-660:2).

UTC asserts a POSA would understand the “claims are drawn to treating *precapillary* PH[.]” Red Br., 50. The specification actually uses the word “precapillary” ***and*** the term “pulmonary hypertension,” but UTC chose to ***claim*** “pulmonary hypertension” without any indication a POSA would artificially limit the claimed phrase to only precapillary PH patients. Appx00166 (9:35-37); Appx00167 (12:64-67); Appx00169 (16:64-65); *cf.* Appx00170 (cl. 1). The court considered and rightly rejected the same arguments UTC presented here in light of the “clear disclosures in the ’793 patent specification[,]” which “expressly includes all five Groups when describing ‘pulmonary hypertension.’” Appx00059-00061. The court also found “the specification does not contain any disclosures which limit the scope of ‘pulmonary hypertension’ to any particular subset of PH patients.” Appx00061. UTC did not disclaim postcapillary PH patients and cannot now, upon realizing the ’793 patent lacks §112 support, seek to avoid invalidity by limiting its

claims post-hoc. *See Network-1 Techs., Inc. v. Hewlett-Packard Co.*, 981 F.3d 1015, 1024 (Fed. Cir. 2020) (where there is no dispute as to the ordinary meaning of a term and neither the claims nor the specification require a departure from the ordinary meaning, the district court erred in excluding embodiments encompassed by the ordinary meaning); *MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012) ("[A] patentee chooses broad claim language at the peril of losing any claim that cannot be enabled across its full scope of coverage.").

II. Liquidia Is Not Liable for Induced Infringement

Liquidia does not have a "belief" of invalidity; it ***knows*** the asserted claims of the '793 patent are invalid under the PTAB's FWD. *See* Red Br., 24-27. Based on this knowledge, *Commil* dictates that Liquidia is not ***liable*** for induced infringement of the '793 patent.

Like the district court, UTC collapsed non-infringement and invalidity into a single issue by requiring "a *final* adjudication" on invalidity, such that collateral estoppel applies. Red Br., 2, 18, 24, 27-31; *see* Appx00054-00057. UTC's position conflicts with Supreme Court precedent acknowledging infringement and validity as "separate issues." *Commil USA, LLC v. Cisco Sys., Inc.*, 575 U.S. 632, 642 (2015). By requiring collateral estoppel, UTC and the district court eliminated the subjective intent element of induced infringement and placed liability solely upon the validity

of the '793 patent. This is legally incorrect and the court's determination that Liquidia is liable for induced infringement of the '793 patent should be reversed.

A. The Supreme Court Distinguished Between a "Belief" and "Knowledge" of Invalidity

Despite acknowledging the question presented to the Supreme Court was "whether knowledge of, or belief in, a patent's validity is required for induced infringement under §271(b)[,]" UTC argues the Court drew no distinction between "belief and knowledge," but instead "between *belief* and *actual invalidity*." Red Br., 25-26. UTC's position is nonsensical—actual invalidity ***is*** "knowledge of … a patent's validity[.]" *Commil*, 575 U.S. at 639. The Supreme Court made clear that "[a]n accused infringer can … prove that patent in suit is invalid; [and] ***if the patent is indeed invalid, and shown to be so under proper procedures, there is no liability***[,]" and provided four examples of how an accused infringer can obtain knowledge of invalidity. *Id*. at 644, 645. Once invalidated by such proper procedures, an accused infringer necessarily ***knows*** of a patent's invalidity and can no longer be liable for infringement.

UTC also incorrectly contends the Supreme Court "flatly rejected the notion that the defendant's mental state as to invalidity had any relevancy to infringement at all." Red Br., 26. *Commil* is premised on the holding in *Global-Tech* that induced infringement requires "proof the defendant knew the acts were infringing. The Court's opinion was clear in rejecting ***any lesser mental state as the standard***."

Commil, 575 U.S. at 642 (citing *Global-Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 2060, 2070-71 (2011)). The relevancy of an accused induced-infringer's mental state (*i.e.*, scienter) was reconfirmed in *Roche Diagnostics Corp. v. Meso Scale Diagnostics, LLC*, where this Court stated "[t]he intent standard for inducement, therefore, 'focuses on, and can be met by proof of, the defendant's subjective state of mind[.]'" 30 F.4th 1109, 1118-19 (Fed. Cir. 2022). Because Liquidia has actual knowledge of the '793 patent's invalidity, it lacks the subjective intent to induce infringement of the '793 patent.

B. Collateral Estoppel is Not Required to Negate Liability

UTC's position is that the PTAB's FWD is not "final," and thus has no collateral estoppel effect on the district court. Red Br., 2, 18, 27-31. *Commil*, however, makes clear that collateral estoppel is not required to negate an accused infringer's liability for induced infringement. Blue Br., 46-54.

1. The PTAB's FWD was Not "Vacated"

UTC asserts that the PTO Director's POP decision "effectively vacated" the PTAB's FWD and that the "PTAB's now-vacated decision" has no effect here. Red Br., 2. But UTC's request for a Precedential Opinion was ***denied***. Appx36654 ("Accordingly, we deny Patent Owner's request for POP review of the Final Written Decision."). UTC's suggestion that the original panel must act on the Director's POP "on rehearing" is wrong. Red Br., 28. The Director stated that "authority over

all issues in this case—including consideration of Patent Owner's pending rehearing request—is returned to the original panel." Appx36654. Thus, the PTAB's FWD is still in effect as the original panel has not granted UTC's rehearing request, and is not required to do so. *Id.*[12]

2. An IPR FWD in 12-18 Months is All that is Required to Negate Liability

UTC ignores the statutory and legal authority confirming the Supreme Court's purposeful reference to an IPR decision in 12-18 months, which establishes that a FWD is all that is needed to remove liability for infringement. Red Br., 2, 27-31; Blue Br., 48-52.

Citing 35 U.S.C. §318(a)-(b), UTC asserts that only "final[ity]" can be a "proper procedure." Red Br., 27-31. Not so. UTC wants this Court to focus on §318, but the Supreme Court has already said the relevant statutory provision is 35 U.S.C. §316, which requires an IPR FWD in 12-18 months. *Commil*, 575 U.S. at 645; Blue Br., 49-50.[13] The Supreme Court's citation to §316, instead of §318, establishes that *Commil* requires only a FWD, not final cancellation of claims under

[12] UTC notes that if a district court's decision on invalidity is reversed, then liability for patent infringement could be reinstated. Red Br., 30. That rationale holds true here. If the '793 FWD is reversed on rehearing or appeal, then Liquidia's liability for infringement of that patent can be reinstated.

[13] Unsurprisingly, UTC failed to address the import of the Supreme Court's reliance on §316.

§318, to negate liability. The Supreme Court is no stranger to §318, having cited it in several cases, including *U.S. v. Arthrex, Inc.*, 141 S. Ct. 1970 (2021). *Id.* at 1978 ("Upon expiration of the time to appeal or termination of any appeal, 'the Director shall issue and publish a certificate canceling any claim of the patent finally determined to be unpatentable…'") (citing §318). In this same decision, §316 was also cited (*id.* at 1977), further demonstrating *Commil's* reliance on §316, and not §318, was purposeful. Moreover, because "finality" was not required by *Commil*, there was no need for the Supreme Court to address "appeals or the precise endpoint when decision becomes 'final[.]'" Red Br., 29-30. Indeed, by not addressing "appeals" or "finality" and only citing §316, the Supreme Court made its position clear—an IPR FWD is sufficient to eliminate liability for induced infringement.

Finally, collateral estoppel would only prevent UTC from re-litigating the validity of the '793 patent. *Papst Licensing GMBH & Co. KG v. Samsung Elecs. Am., Inc.*, 924 F.3d 1243, 1250-51 (Fed. Cir. 2019). Whether UTC is prevented from later asserting the '793 patent is valid has no bearing on Liquidia's current "subjective" state of mind regarding liability for induced infringement. Because the PTAB's FWD invalidated all asserted claims of the '793 patent, the *Commil* decision establishes that Liquidia is not liable for induced infringement of the '793 patent, and the district court's decision should be reversed.

III. TN is Not a Proxy for LIQ861 Bulk Powder

UTC confirms that to prove infringement of claims 1-3 of the '066 patent, the only evidence it presented at trial compared TN02 to TN, neither of which are the "pharmaceutical composition" of claim 1. Red Br., 52-56. Accordingly, there is no evidence that Liquidia's LIQ861 bulk powder, identified by UTC as the "pharmaceutical composition," meets the limitations of these asserted claims.

With this evidentiary failing, UTC doubles down on the analysis conducted by its expert, Dr. Nuckolls, comparing the impurities resulting from alkylation and hydrolysis in TN02 and TN. Red Br., 52-55. This comparison, however, fails to consider that TN is first dissolved (where it dissociates into ions, one of which is treprostinil free acid), and TN is not present in the LIQ861 bulk powder. Blue Br., 54-55, 57, 59; Appx00027; Appx13137 (447:20-448:23); Appx13137 (450:1-15); Appx13211 (741:7-16); Appx14131-14144. Liquidia's PRINT process, which uses TN as a starting material, refers to "treprostinil sodium" only prior to dissolving TN, and thereafter refers to "treprostinil." Appx14132-14133. Because UTC's infringement evidence for claims 1-3 relies solely on an analysis of TN02 and TN, and UTC presented no evidence regarding impurities in the LIQ861 bulk powder, UTC has not met its evidentiary burden on infringement. Appx13055 (122:24-123:1). Accordingly, the district court's factual findings on infringement of claims 1-3 were clearly erroneous.

UTC excuses Dr. Nuckolls' failure to compare TN02 to LIQ861 bulk powder by pointing to his testimony that it would be difficult to conduct the comparison required by the claims. Red Br., 55. This is a claim drafting issue and mischaracterizes Dr. Nuckolls' testimony. He testified that conducting the comparison required by the claims would be difficult "without samples." Appx13058 (133:22-134:8). UTC received samples of the LIQ861 bulk powder, but withheld them from its expert. [14] Appx11844-11846; Appx11906-11914; Appx11937-11956.

UTC also asserts the court determined that TN is a proper proxy for LIQ861 bulk powder because Liquidia's processing of TN does not affect the impurities generated from alkylation and hydrolysis. Red Br., 56-58. UTC and the district court overlook the fact that TN is not in LIQ861 bulk powder and, therefore, whether Liquidia's "processing" affects the impurities of TN is not the relevant question. To be a proper proxy, TN needs to be "representative of the accused product." *Ferring B.V. v. Watson Lab'ys, Inc.-Fla.*, 764 F.3d 1401, 1409-10 (Fed. Cir. 2014) (reversing a finding of infringement because the outlier products used to prove infringement "were not representative of [defendant's] ANDA product"); Red Br., 58. Dr. Nuckolls performed no evaluation as to whether the TN is representative of the

[14] UTC fails to address the fact Liquidia provided samples of LIQ861 bulk powder.

accused product. This renders irrelevant Dr. Nuckolls' speculative testimony that he "wouldn't expect" Liquidia's PRINT process to impact impurities. Appx13064 (157:7-17); Red Br., 55.

UTC notes that Liquidia relies on Yonsung's DMF "for all treprostinil drug ***substance*** information[,]" implying that stability data permits LIQ861 bulk powder to be stored at ambient temperature. Red Br., 57-58. But LIQ861 bulk powder, the accused "pharmaceutical composition," ***is not*** the drug substance and, nonetheless, TN is stored at 2ºC-8ºC according to the DMF. Appx14132-14138; Appx07590; Appx13211 (741:1-19); Appx13137 (448:6-23).

Finally, UTC's attempt to distinguish *Ferring*, *Kim*, and *Morton* are unavailing. Red Br., 58-59. In *Ferring*, the district court relied on testing of four tablets of the accused product. *Ferring*, 764 F.3d at 1409-10. Although those four tablets were "atypical," Ferring provided data from those four tablets in an attempt to establish they were representative of all accused products. Here, UTC prevented its expert from generating this data, depriving the district court the opportunity to evaluate whether TN is truly representative of LIQ861 bulk powder. In *Kim*, Kim used a proxy that was allegedly representative of ConAgra's 7-Grain and Whole Wheat products. *Kim v. ConAgra Foods, Inc.*, 465 F.3d 1312, 1319-20 (Fed. Cir. 2006). This Court determined Kim's proxy was not representative of the accused products because those products contained additional ingredients taking it outside of

the "consisting essentially of" claim limitation, and Kim's expert testimony otherwise was "conclusory" and not supported "with any examinations or tests of the accused products." *Id.* at 1320. The same holds true here: TN is dissolved and combined with other excipients to make LIQ861 bulk powder, and Dr. Nuckolls' "wouldn't expect" testimony was conclusory in nature and not supported by testing of the accused LIQ861 bulk powder—testing UTC could have had done. Finally, UTC contends that in *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 959 F.2d 948 (Fed. Cir. 1992), non-infringement was based on "no objective support for the actual existence" of the claimed compounds. Red Br., 58. That finding was based on actual testing of the accused product—again, testing UTC and its expert did not do here. *Morton*, 959 F.2d at 951.

The court's determination that Liquidia infringes claims 1-3 of the '066 patent was clearly erroneous and should be reversed.

COUNTER-STATEMENT OF THE ISSUES ON CROSS-APPEAL

1. Whether the district court clearly erred in finding product-by-process claims 1-3 and 6 of the '066 patent invalid, when the unrebutted evidence demonstrates there is no structural or functional difference between the claimed composition and the composition disclosed in Moriarty 2004.

2. Whether the district court clearly erred in finding that Liquidia will not infringe claims 6 and 8 of the '066 patent when Yonsung's DMF and Liquidia's

NDA require TN (treprostinil sodium) to be stored at 2º-8ºC, not at ambient temperature.

3. Whether the district court clearly erred in finding that Liquidia will not infringe claim 8 of the ’066 patent when TN is not stored during Liquidia’s PRINT process.

COUNTER-STATEMENT OF THE CASE ON CROSS-APPEAL

I. Relevant Claims of the ’066 Patent

UTC’s cross-appeal contests the district court’s determinations regarding claims 1-3, 6, and 8 of the ’066 patent. *See* Red Br., 14-17; *id.* n.1. Independent claim 1 and its dependent claims (claims 2, 3, and 6) are product-by-process claims directed to a “pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof” made by a specific process. Appx00121-00132. This process involves alkylating benzindene triol (BTO), hydrolyzing the resulting product to form a starting batch of treprostinil, and then forming a salt that is either itself the claimed final pharmaceutical composition or is used to regenerate treprostinil free acid as the final pharmaceutical composition. Appx00132 (cl. 1).

Claims 1-3 and 6 also require the following process step: “a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps … whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition, and wherein said

alkylation is alkylation of benzindene triol."[15] Appx00132 (cl. 1). Relevant to the cross-appeal, dependent claim 6 recites "wherein the isolated salt is stored at ambient temperature." Appx00132 (cl. 6). Similarly, independent claim 8 is a process claim that requires "storing the treprostinil salt at ambient temperature" before it is used. Appx00132 (cl. 8).

II. The District Court Correctly Found that Moriarty 2004 Discloses the Same Composition as the '066 Patent

The court's decision found clear and convincing evidence that product-by-process claims 1-3 and 6 are invalid because they claim the same composition disclosed in Moriarty 2004. Appx00038-00045.[16] The decision rested on seven findings of fact: (1) "[t]he priority date of the '066 patent is December 17, 2007"; (2) "[t]reprostinil is also known as UT-15 or treprostinil free acid"; (3) "[Moriarty 2004] teaches the synthesis of 99.7% pure treprostinil free acid, via alkylation and hydrolysis"; (4) "Moriarty [2004] is prior art"; (5) "[t]he UT-15 treprostinil taught by Moriarty [2004] is the same chemical structure as the treprostinil product of claims 1-3, 6, and 9 of the '066 patent"; (6) "[t]he average purity of UTC's batches of UT-15 treprostinil made by Moriarty [2004] and the '066 process are the same:

[15] For ease of review, this Brief will refer to this limitation as the "impurities-lowering" limitation. *See also* Red Br., 20.

[16] The district court also found claim 9 invalid for the same reason, but claim 9 is not at issue in UTC's cross-appeal. Red Br., 17 n.1.

99.7%"; and (7) "[t]here are no structural or functional differences between the UT-15 treprostinil taught by Moriarty [2004] and the treprostinil claimed in the '066 patent." Appx00038-00039. UTC has not demonstrated any clear error in these findings.

The court correctly found that the claimed "pharmaceutical composition[] comprising treprostinil" can be treprostinil alone (*i.e.*, treprostinil free acid), foreclosing UTC's argument that "Moriarty [2004] cannot invalidate the product-by-process claims because it only discloses treprostinil [free acid.]" Appx00040; Appx29406; Appx30259; Appx13127 (408:16-17); Appx13140 (459:5-6, 461:5-6); Appx13211 (742:5-9). The court then relied on Dr. Winkler's unrebutted testimony that the claimed composition and the Moriarty 2004 composition are the same. Appx00041-00043; Appx00043 ("No UTC expert or fact witness rebutted Dr. Winkler's opinions[.]"). The court explained that the claimed impurities-lowering limitation "is a process limitation" that "merely describes the process and does not impart any structural or functional differences in the claimed pharmaceutical composition[.]" Appx00041 n.15; *see also* Appx00041 (finding that claims 1-3 and 6 "do not claim any purity percentage, impurity profile, or commercial scale production").[17]

[17] Likewise, it is irrelevant for purposes of invalidity that "[e]veryone agrees that Moriarty 2004 did not disclose any salt-formation step" (*see* Red Br., 17), because invalidity is based on the "product"—not the process—and salt formation is a

The court rejected UTC's attempt to show a structural or functional difference. Appx00043-00045. Dr. Walsh only "compared the treprostinil ***free acid*** prepared at the Chicago facility and the treprostinil ***diethanolamine salt*** prepared by the '066 process" (Appx00044), and conceded that treprostinil salt is a ***different*** compound than treprostinil free acid. Appx13227 (804:17-19). Thus, his testimony "fail[ed] to identify any structural or functional differences between the treprostinil products." Appx00044.

Consistent with the plain language of the claims, the court found the claims do not recite any purity percentage or impurity profile, and do not identify any specific impurity in the treprostinil product. Appx00041; Appx13140 (460:8-16); *see also* Appx13051 (105:19-106:20). Although the claims do not require any purity level, the specification states that the treprostinil generated by the claimed process can have a purity ranging from 99.7% to 99.9%, and could be as low as 90%. Appx00041; Appx00128 (9:22-23); Appx00130 (14:55-65); Appx13226-13227 (803:13-804:16). Nor do the claims cover any stability or storage of the final treprostinil product. Claim 6's limitation reciting "wherein the isolated salt is stored at ambient temperature" concerns only the intermediate salt generated during the

process step. Nonetheless, the salt formation step does not impart any structural or functional differences in the claimed pharmaceutical composition. *See* Appx00041 n.15.

process steps. Appx00132 (17:51-18:28, 17:34-35, 17:62-63); Appx13267 (964:19-965:6).

The court found Moriarty 2004 teaches synthesis of treprostinil free acid (*i.e.*, UT-15) with a purity of 99.7%, by alkylation and hydrolysis of BTO. Appx00039 (Findings of Fact 2 and 3); Appx29406; Appx29413; Appx29418; Appx13140 (460:25-462:14). The treprostinil disclosed in Moriarty 2004 has the same chemical structure as the treprostinil of claims 1-3 and 6, and its 99.7% purity—though not required by the claims—falls within the disclosure of the '066 patent specification. Appx00039 (Findings of Fact 5 and 6); Appx13139-13145 (457:6-480:2); Appx13140-13141 (462:25-463:2); Appx13142 (467:3-5); *compare* Appx29408 (depicting the chemical structure of UT-15 treprostinil as compound 7), *with* Appx00128 (10:55-65 (depicting the chemical structure of UT-15 treprostinil)); *compare* Appx29418 ("purity 99.7%"), *with* Appx00130 (14:55-65 (purities ranging between 99.7% and 99.9%)); Appx13226-13227 (803:16-804:16).

The court also relied on UTC's statements ***to the FDA*** that the product made according to the process claimed by the '066 patent (*i.e.*, the new Silver Spring process) was the "same" as and "equivalent" to the product made according to Moriarty 2004 (*i.e.*, the former Chicago process), and had the same specification limits. Appx00041-00043 (citing Appx13141 (463:20-22, 464:15-465:2), Appx13142-13145 (467:17-468:3, 469:7-14, 470:21-473:5, 473:16-477:18, 478:23-

479:21)); Appx28389 ("[T]he lots of treprostinil API produced by the new process in Silver Spring are of the ***same* high quality and purity** as the commercial lots of API produced by the existing process at the Chicago facility."); Appx29861 ("The release data for the drug substance batch prepared by the revised route of synthesis indicate that it is of ***equivalent* quality** to the batches produced by the current synthetic route, ***particularly with respect to the assay and purity profile***."); Appx29884-29885 ("[T]he simplified chemical synthesis of treprostinil will provide API that meets the ***same* acceptance criteria** as API obtained from the 20-step chemical synthesis, with a ***very similar impurity profile*** and similar acceptable criteria."); *compare* Appx29050 ('066 Product Certificate of Analysis from 2020) *and* Appx29874-29875 ('066 Process Optimization Batches Release Testing Data), *with* Appx29876 (Moriarty Release Testing Data).

The district court found claims 1-3 and 6 of the '066 patent invalid because "there is no record evidence that contradicts Dr. Winkler's testimony that the claimed treprostinil product and Moriarty UT-15 treprostinil are the same," and because "[t]here are no structural or functional differences" between the two. Appx00039 (Finding of Fact 7); Appx00045.

III. The District Court Correctly Found that Liquidia Will Not Infringe Claims 6 or 8 of the '066 Patent

The court found UTC failed to prove that Liquidia's proposed LIQ861 product will infringe claims 6 and 8 of the '066 patent, both of which require storing

treprostinil salt at "ambient temperature" before use. Appx00022-00025; Appx00031-00038. This decision was based on three findings of fact: (1) "Liquidia's NDA and Yonsung's DMF require treprostinil sodium to be stored at 2°C to 8°C"; (2) "Liquidia will not use treprostinil sodium batches which have been stored at ambient temperature for GMP manufacturing"; and (3) "Liquidia begins preparing a pharmaceutical product during Step 1 of its PRINT process." Appx00025.

Addressing UTC's contention that Liquidia only "promises" not to infringe, the court found that "Liquidia has represented to the FDA that it will store treprostinil sodium between 2°C and 8°C" and that "UTC has failed to prove that Liquidia will go against these representations." Appx00031-00036. The district court also relied on the testimony of Liquidia's Executive Director of Analytical Operation, Mr. Kindig, to find that Liquidia will not use out-of-specification batches in GMP manufacturing to make a "pharmaceutical composition" of claim 6. Appx00034; *see also* Appx00033-00036 (rejecting UTC's other arguments regarding temperature excursions).

Regarding claim 8, reciting "preparing a pharmaceutical product," the court further found that "a POSA would understand that Liquidia begins preparing the LIQ861 product at PRINT Step 1, not Step 5." Appx00037. Thus, "any 'storage' between steps in the PRINT process [] cannot meet the limitations of claim[] 8 [],

which require[s] storage before preparing a pharmaceutical product." *Id.*; *see also* Appx00036.

SUMMARY OF ARGUMENT ON CROSS-APPEAL

This Court should affirm the district court's invalidity and non-infringement findings with respect to the '066 patent for the following reasons:

1. UTC cannot show that the court legally erred in finding claims 1-3 and 6 ("the product-by-process claims") of the '066 patent invalid because they claim the same product made according to Moriarty 2004. The court correctly found that the claimed "pharmaceutical composition[] comprising treprostinil" can be treprostinil free acid alone, and the unrebutted evidence of record demonstrates that there is no structural or functional difference between the claimed treprostinil free acid and the treprostinil free acid disclosed in Moriarty 2004. UTC's arguments regarding the purported "specific impurities" in the claimed composition fail because (a) the product-by-process claims do not require any purity level or specific impurity, and (b) the impurities-lowering limitation is a process step that does not define the claimed composition.

2. The court did not err in holding that claims 6 and 8 of the '066 patent were not infringed. Per Liquidia's NDA, TN is never stored at ambient temperature. Consistent with FDA regulations, the NDA's storage specifications are strict regulatory requirements, not mere recommendations. UTC's counterarguments that

the district court erroneously construed "storage" as impossible during the later stages of the PRINT process, and that ambient storage occurs between Steps 1-4 of the PRINT process, are both unavailing. A review of Liquidia's NDA makes clear that use, and not storage, of TN begins immediately at Step 1 of the PRINT process. Because the district court's finding of noninfringement of claims 6 and 8 of the '066 patent is supported by substantial evidence, it should be affirmed.

ARGUMENT ON CROSS-APPEAL

I. Claims 1-3 and 6 of the '066 Patent Are Invalid Because They Claim the Same Composition in Moriarty 2004

"In determining validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1369 (Fed. Cir. 2009). This is because of the "long-standing rule that an old product is not patentable even if it is made by a new process." *Id.* at 1370. Accordingly, "[i]f the product in a product-by-process claim is the same as [*i.e.*, anticipated by] or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985). An exception to this well-known principle is if the patentee can show that "the process by which a product is made imparts 'structural and functional differences' distinguishing the claimed product from the prior art[.]" *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1268 (Fed. Cir. 2012) (citation omitted); Appx13267 (963:6-11). UTC has failed to show the

claimed treprostinil free acid is structurally or functionally different from the treprostinil free acid of Moriarty 2004.

UTC's cross-appeal concerning the invalidity of the '066 patent's product-by-process claims relies upon (1) process limitations, not product limitations, and (2) alleged structural and functional differences between a compound that is ***different*** from the prior art Moriarty 2004 compound and not the treprostinil free acid claimed. No witness rebutted the testimony of Liquidia's expert, Dr. Winkler, and Dr. Walsh, UTC's fact witness on this issue, provided an irrelevant comparison of different compounds. Appx00043-00044. UTC's cross-appeal raises no factual or legal error in the court's decision and, accordingly, it should be affirmed.

A. Treprostinil Free Acid is a "Pharmaceutical Composition Comprising Treprostinil"

UTC asserts that claims 1-3 and 6 recite "a pharmaceutical composition containing treprostinil ***and the unexpectedly reduced levels of certain impurities*** that remain after a novel process of purification by salt formation." Red Br., 75. This is not the claim language. The "product" portion of the claim merely recites "[a] pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof[.]" Appx00132 (cl. 1). The claim term "comprising," which UTC ignores, permits other components but does not require them. As the court properly found, the treprostinil free acid of Moriarty 2004, meets the claim. *See In re Thomas*, 714 F. App'x 1005, 1008 (Fed. Cir. 2017) ("What the prior art discloses

is [] a question of fact.") (citing *Para-Ordnance Mfg., Inc. v. SGS Importers Int'l, Inc.*, 73 F.3d 1085, 1088 (Fed. Cir. 1995)).

Moreover, while UTC contends the district court "misconstrued" the "pharmaceutical composition" term and "ignored" the intrinsic evidence (Red Br., 78, 81), UTC never requested construction of this phrase, let alone a construction that requires more than treprostinil. UTC does not address the court's findings that the '066 patent specification provides no distinction between treprostinil and a pharmaceutical composition comprising treprostinil, and only describes process steps for synthesizing treprostinil or its salt. Appx00040. The court determined that, based on the claim's plain language, the limitation reciting "[whereby a] level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition" is merely a process step comparing the "starting batch" to the pharmaceutical composition. Appx00041 n.15. No UTC witness supported UTC's position that this language is a "product" limitation as opposed to a process step. Its experts Drs. Toste and Nuckolls actually confirmed that the impurities-lowering limitation requires the process step of ***comparing*** a process intermediate (the starting batch of treprostinil) to the pharmaceutical composition. Appx13068-13075 (175:8-25, 181:4-182:1, 188:2-8, 199:10-202:19); Appx13051-13052 (108:4-110:1).

UTC's reliance on the prosecution history of the '066 patent is unavailing. Red Br., 80-81. Allowance of the '066 patent claims, based on *ex parte* prosecution without the benefit of countervailing evidence and testimony, does not confirm the claimed "pharmaceutical composition" includes a reduction in impurities. UTC never told the PTO that the data it submitted from the '393 IPR was found unconvincing and that the PTAB invalidated the '393 patent—the Examiner's rejection over Moriarty was withdrawn on November 30, 2016, and the '066 patent allowed on January 30, 2017, ***before*** the '393 patent FWD issued on March 31, 2017. Red Br., 80; Appx32016, Appx32018; Appx36657-36663; Appx05949, Appx05982-05991 (comparing batches of treprostinil made according to Moriarty 2004 to the process of the '393 patent and concluding no structural or functional differences). UTC failed to disclose those facts here as well.[18]

UTC also ignores the testimony of its own expert, Dr. Nuckolls, who confirmed that the claimed "pharmaceutical composition" "could be [t]reprostinil or the pharmaceutically acceptable [salt thereof.]" Appx00040; Appx13050-13051 (104:22-105:8). Dr. Winkler agreed.[19] Appx13140 (462:15-24). And the parties'

[18] UTC's argument regarding the Board's denial of institution for the '066 IPR is misplaced because the Board has broad discretion to institute or deny IPR petitions, and a decision to institute is preliminary—not final. *Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. 261, 273 (2016).

[19] Citing to Dr. Winkler's non-infringement testimony, UTC conflates proof necessary to establish ***infringement*** of a product-by-process claim, where process

experts agreed that the claims do not require any purity or impurity level in the final pharmaceutical composition. Appx13140 (460:8-16); Appx13051 (105:19-106:20); *see also* Appx00041. Accordingly, the court properly determined that treprostinil free acid meets the "pharmaceutical composition comprising treprostinil" limitation.

B. UTC Improperly Focuses on Process Steps

UTC spends pages asserting that the purported "specific impurities" or "relevant impurities" confer a structural or functional difference sufficient to distinguish the claimed product from the Moriarty 2004 product. Red Br., Sections VI.A-C; *see also id.* at 75-76. UTC ignores the claimed product, and instead touts the alleged process benefits. Red Br., 76 ("[T]his ***process*** is particularly effective at removing synthetic impurities generated during alkylation and hydrolysis that are difficult to remove using prior-art methods[.]").[20] In doing so, UTC ignores that "an old product is not patentable ***even if*** it is made by a new process." *Amgen*, 580 F.3d at 1369-70; *see also In re Thorpe*, 777 F.2d at 697. UTC's conclusions regarding how this process allegedly impacts the claimed product are wholly unsupported attorney argument. *E.g.*, Red Br., 76 ("The resulting pharmaceutical composition

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steps are relevant, and proof necessary to ***invalidate*** a product-by-process claim, where the process steps are not relevant. *See* Red Br., 79.

[20] *See also id.* at 75 ("a ***novel process*** of purification by salt formation"); *id.* at 84-85 ("unlike traditional column chromatography purification ***methods***, the claimed ***salt-formation process*** was able to effectively separate treprostinil from impurities"); *id.* at 85 ("the '066 Patent's ***novel salt-formation process***").

will therefore have lower levels of these synthetic impurities than a pharmaceutical composition of treprostinil purified using traditional methods.") (no citation).[21] Plainly, it does not matter that Moriarty 2004 "does not teach purification through salt formation[,]" because that is a process step and need not be disclosed to invalidate a product-by-process claim. *See id.* at 76.

UTC asserts that Moriarty 2004 "provided *no* disclosure about the level of these or any other specific impurities" resulting from alkylation or hydrolysis. Red Br., 83. But the '066 patent suffers from this same "silence." The '066 patent specification does not identify any impurity generated by alkylation or hydrolysis, nor any impurity removed upon salt formation. Appx00121-00132. Dr. Winkler and UTC's expert, Dr. Toste, confirmed this fact. Appx13146 (485:24-486:1); Appx13071-13072 (188:18-189:17); Appx13147 (489:10-15); Appx13145 (481:17-19). Named inventor, Dr. Batra, also confirmed the patent does not disclose any impurity generated or removed. Appx13161-13162 (546:15-548:15); Appx13163 (552:3-554:1). UTC is in no position to complain about the disclosure of Moriarty 2004, when its own patent is similar. Regardless, there are no actual differences as

[21] *See also id.* (asserting without citation that "the claims conferred [critical structural features] on the resulting product"); *id.* at 81 (asserting without citation that "the claim elements concerning 'impurities' … require differences in the structure of the resulting product that are integral to discerning the scope and content of the claimed 'pharmaceutical composition'").

the specification permits as low as 90% purity (Appx00128 (9:22-23)), whereas Moriarty 2004 composition is 99.7% pure. Appx29418.

UTC complains that Liquidia only assessed the "overall purity" of the "treprostinil compound" (Red Br., 76-77, 83-84)—but the '066 patent does the same. The specification states "the product of the process … has higher purity[,]" without specifying what impurities were allegedly removed, or where they came from. Appx00126 (5:66-67). None of the Examples disclose "specific" impurities that are generated or removed. Examples 5 and 6 only provide overall purity data and do not identify the removal of any "specific impurity" resulting from alkylation and hydrolysis. Appx00130 (14:55-65); Appx00132 (17:26).[22] UTC cannot keep secret the specific impurities its process allegedly removes, but then complain that the prior art fails to reveal those secrets.[23]

[22] Examples 1-4 do not provide any purity or impurity information. Appx00128-00130 (9:45-13:67).

[23] UTC further asserts that "[o]verall purity is not the distinguishing feature of the product claimed by the patent" because, "as the district court expressly found elsewhere, the invention is a pharmaceutical composition with a reduction in *specific impurities*—those resulting from alkylation and hydrolysis steps—after salt formation." Red Br., 83-84 (citing Appx00025). But this argument refers to the district court's ***infringement*** analysis, and thus again conflates proof necessary to establish infringement of a product-by-process claim and proof necessary to invalidate a product-by-process claim. *See* Appx00025.

Responding to UTC's contention that Moriarty 2004 does not disclose a "pharmaceutical composition" with the "relevant impurities" (*e.g.*, Red Br., 82-83), that composition is in fact disclosed. Moriarty 2004 made "crude UT-15" (treprostinil) by alkylation and hydrolysis process steps resulting in the claimed "starting batch." Appx29418 (right column); Appx13140 (460:25-462:14); Appx13155 (519:18-22, 520:9-21). That "crude" treprostinil starting batch was then purified to give "pure UT-15" (the pharmaceutical composition) with a purity of 99.7%. Appx29418 (right column); Appx13143-13144 (473:16-477:18). Thus, the "starting batch" of treprostinil in Moriarty 2004 includes impurities from alkylation and hydrolysis that are removed upon further processing. And Moriarty 2004's 99.7% pure treprostinil falls within the '066 patent's disclosure that treprostinil can have a purity as low as 90%, and matches Example 5's disclosure of 99.7% purity for treprostinil free acid made according to the invention. Appx00041; Appx00128 (9:22-23), Appx00130 (14:55-65); Appx13226-13227 (803:13-804:16).

UTC relies on *In re Nordt Development Co.*, 881 F.3d 1371 (Fed. Cir. 2018) to argue that the "structural elements of the claimed 'pharmaceutical composition' are apparent from the express impurities-reducing claim language" (Red Br., 79; *see also id.* at 81)—but *Nordt* is not applicable here. Red Br., 79, 81. There, the patent application was directed to an elastic knee brace, and the claim term "injection molded" was found to connote a specific structure. 881 F.3d at 1375. Here, the

impurities-lowering limitation is nothing like the "structural" limitations identified in *Nordt* and relates only to a comparison of impurities during the claimed process and not any level of impurities in the final product. *Id.* at 1375-76 (finding that "injection molded" connotes structure and identifying "chemically engraved," "integral," "superimposed," and "a molded plastic" as examples of structural terms rather than process terms) (citations omitted). Regardless, the '066 specification never imparts a structural meaning to the impurities-lowering limitation as the specification in *Nordt* did. *Id.*; *cf., e.g.,* Appx00132 (17:29-32) (merely stating that "[t]he impurities carried over from intermediate steps … are removed during the … salt formation step"); *see also supra* pp. 37-38.[24]

Likewise, the claims at issue in *Amgen* are distinguishable from the product-by-process claims here. Red Br., 82. In *Amgen*, actual structural differences were described in the specification. 580 F.3d at 1367 (referring to "studies" in the

[24] *Kamstrup A/S v. Axioma Metering UAB*, 43 F.4th 1374 (Fed. Cir. 2022) and *Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345 (Fed. Cir. 2016) also do not help UTC. Red Br., 78, 81. As in *Kamstrup*, UTC "has not identified disclosure in the specification or prosecution history or extrinsic evidence evidencing structural and functional differences," and "the alleged structural and functional difference that [UTC] identifies is detached from the claims." 43 F.4th at 1382-83 (affirming invalidity finding); *see supra* pp. 25-29. As in *Purdue*, the impurities-lowering limitation here "does not describe the structure of [the claimed pharmaceutical composition] and thus is a process limitation." 811 F.3d at 1353-54 (affirming invalidity finding); *see also id.* at 1353 ("Purdue claimed the end product; it did not claim a particular method for creating that product[.]"); *see supra* pp. 25-29.

specification regarding structural differences); *see also id.* ("At trial, Amgen's expert … testified at length regarding differences in the ***carbohydrate composition*** of [the claimed compound] and [the prior art]."). Here, the specification does not refer to any studies indicating a difference in ***composition*** between the claimed treprostinil and the Moriarty 2004 treprostinil, and Dr. Walsh did not compare like compounds, as was done in *Amgen*. *See id.*; *e.g.*, Appx00131-00132 (merely comparing the process steps and overall purity of the treprostinil composition made according to the claimed process and the prior art process); *see supra* pp. 26-27. UTC told the FDA that the two processes produced products of the "same" and "equivalent" purity, and its own data (presented by Dr. Winkler at trial) showed that the average purity of the resulting products is the same (99.7%). *See supra* pp. 27-29. Thus, unlike the claims in *Amgen*, 580 F.3d at 1381-82, the impurities-lowering limitation here is a process step that imparts no structural or functional difference on the claimed treprostinil product. *See supra* pp. 25-29.

C. There is No Structural or Functional Difference between the Claimed and Previously-Disclosed Treprostinil Free Acid

No UTC expert or fact witness testified that there was a structural or functional difference between Moriarty 2004 treprostinil and the claimed treprostinil.[25] *See* Appx00043. Indeed, no UTC witness testified about Moriarty

[25] UTC states that "[t]he court did not address or make any findings comparing the levels of any particular impurities (*e.g.*, the synthetic impurities resulting from the

2004 or the UT-15 treprostinil it discloses, much less compared it to the claims. *See id*. Instead, pointing to the testimony of Drs. Walsh and Toste, UTC attempts to compare treprostinil salt to treprostinil free acid and argue there are structural and functional differences between the two. *See* Red Br., 84-86. But, as the court found, this comparison is insufficient to support the validity of the '066 claims. Appx00043-00044. Dr. Walsh testified, unequivocally, that the treprostinil diethanolamine salt he relied on is a ***different compound*** from Moriarty 2004 treprostinil free acid. Appx13227 (804:17-19); Appx00044. UTC ignores Dr. Walsh's admission.

Dr. Toste's testimony was directed to infringement, not validity. Nonetheless, he focused on the alleged advantages of the claimed ***process*** of salt formation compared to prior chromatography purification processes. Red Br., 84-85. Dr. Toste never compared impurity profiles of any claimed compound to the prior art,

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alkylation and hydrolysis steps) in the product obtained from Moriarty 2004 to those obtained from the salt-formation process recited in the '066 Patent claims." Red Br., 17. This misunderstands the point. The court did not need to make this comparison because it found that the claimed "composition comprising treprostinil" can be treprostinil free acid (*see* Appx00040), and "[t]he UT-15 treprostinil [free acid] disclosed in Moriarty has a purity of 99.7%, which falls within the disclosures of the '066 patent specification" regarding the "purity of [treprostinil free acid]" (Appx00041 (second brackets in original)). In any event, as the district court found, "UTC has not provided any evidence or expert testimony which compares the claimed treprostinil free acid to the Moriarty UT-15 treprostinil, instead choosing to focus on the claimed treprostinil salt." Appx00044-00045.

and UTC does not assert otherwise. Any difference in the 3AU90 impurity is irrelevant because Dr. Toste never compared this treprostinil to the prior art, and the claims do not specify this impurity. *See supra* pp. 27-28, 42; Red Br., 85.

As noted, Dr. Walsh's testimony fails to identify any structural or functional difference because, as UTC admits (Red Br., 85-86), he compared Moriarty 2004 treprostinil ***free acid*** made in UTC's Chicago facility to treprostinil diethanolamine ***salt***, which are different compounds. Appx13225-13227 (799:1-804:16 (discussing Appx13357-13362)).[26] UTC argues that the court erred in dismissing Dr. Walsh's testimony because its reasoning was "internally inconsistent" with how it treated Dr. Winkler's testimony. Red Br., 85-86. Not so. The court, relying on Dr. Winkler, explained over several pages why there was no structural or functional difference between the claimed "pharmaceutical composition comprising treprostinil" and Moriarty 2004 treprostinil free acid. Appx00041-00044. This explanation included Dr. Winkler's testimony concerning the identical structure and purity profile of the claimed treprostinil free acid and Moriarty 2004 treprostinil free acid. Appx00041

[26] Both the PTAB and Federal Circuit considered similar testimony from Dr. Walsh, including testimony regarding the 3AU90 impurity, and concluded "the comparisons of purity data for Moriarty and '393 patent treprostinil set forth in the Walsh Declaration and in the specification of the '393 patent itself similarly indicate that batch-to-batch variation, rather than any structural or functional difference between treprostinil products, accounts for the reported differences in overall purity and impurity profile." *SteadyMed Ltd. v. United Therapeutics Corp.*, IPR2016-00006, 2017 WL 1215714, at *15 (P.T.A.B. Mar. 31, 2017). The '066 and '393 patents share the same specification. *Compare* Appx00121-00132, *with* Appx29030-29045.

(citing Dr. Winkler's testimony at Appx13139-13145 (457:6-480:2)). The court also relied the fact that upon changing facilities from Chicago (Moriarty 2004 process) to Silver Spring ('066 process), UTC told the FDA that the treprostinil free acid made according to the '066 process was "equivalent," with respect to purity, to the treprostinil free acid made according to Moriarty 2004 such that they had the same impurity profiles. Appx00042 (citing Dr. Winkler at Appx13141 (464:15-465:2)); Appx28389; Appx29861; Appx29884-29885; Appx00043 (citing Dr. Winkler at Appx13142-13143 (469:15-471:23)). UTC never informed the FDA that upon this change in processes, the treprostinil "was safer, less toxic, or purer than" treprostinil made according to Moriarty 2004. Appx00042. UTC points to no internal inconsistencies with these findings (Red Br., 85-87), which alone are sufficient to find the product-by-process claims invalid.

Despite this unrefuted evidence, UTC contends "Dr. Winkler assumed treprostinil salt and treprostinil free acid are comparable." Red Br., 86. But Dr. Winkler never compared the purity of treprostinil free acid to treprostinil salt, and UTC cites no evidence that he did. UTC now presents, for the first time, six lines of testimony from its own witness, Dr. Robert Williams, in the '393 IPR proceeding to assert that the data Dr. Winkler relied on included "some batches of just salt, but most of them are acid." *Id.*; Appx29986 (100:4-9). UTC never raised this issue with the district court in its post-trial briefing, and the argument is thus waived. *E.g.*,

Finjan, Inc. v. Secure Computing Corp., 626 F.3d 1197, 1208 (Fed. Cir. 2010) (finding argument waived when not raised in post-trial motions). Nonetheless, Dr. Williams in the '393 IPR did not compare a treprostinil salt to a treprostinil free acid, but instead was attempting to compare free acid to free acid because "most" of the batches were the free acid. Appx29986 (100:4-9). Dr. Walsh, on the other hand, did not compare treprostinil free acid made according to the claims to any other treprostinil free acid ***at all***. Moreover, based on comparing commercial batches of Moriarty 2004 treprostinil free acid to commercial batches of the '393/'066 patent treprostinil free acid, the PTAB found that "Moriarty [2004] treprostinil exhibit[s] impurity profiles nearly identical, ***if not superior***, to those seen in individual commercial batches of '393[/'066] patent treprostinil[,]" and had a "higher overall purity." Appx05986-87. Thus, the court did not treat Dr. Winkler and Dr. Walsh inconsistently.

UTC also asserts that the court's "comparisons between treprostinil salt and a final treprostinil product" for purposes of assessing ***infringement*** is internally inconsistent with its findings concerning Dr. Walsh's comparison. Red Br., 86-87 (citing Appx00025). For UTC's position to make any sense, it must be admitting that the LIQ861 bulk powder made from treprostinil sodium no longer contains TN. If so, this supports Liquidia's position that UTC improperly relied on treprostinil sodium as a proxy for LIQ861 bulk powder for purposes of infringement. *See supra*

pp. 20-23. Regardless, UTC cannot point to evidence UTC relies on for infringement of a product-by-process claim to support the validity of that claim.[27]

UTC's argument that "[c]omparisons between UTC's commercial processes were irrelevant to anticipation by Moriarty 2004" contradicts the extensive evidence of record confirming that UTC's "Chicago process" and "Moriarty 2004 process" are the same. *See* Red Br., 87-89; Appx00041-00043; Appx00041-00042 n.16. Contrary to UTC's assertion, the district court did not merely "accept[] conclusory testimony of Dr. Winkler that the Chicago process was the process disclosed in Moriarty 2004" (Red Br., 87-88); it also relied on Dr. Winkler's comparison of Moriarty 2004 to the Chicago process, as well as the testimony of '066 inventor Dr. Batra. Appx00041-00042 n.16 (citing Appx13161 (546:2-10), Appx00124 (1:28-31)). The court also noted that no UTC witness refuted Dr. Winkler, and that UTC's witness Dr. Walsh also equated the Chicago process with Moriarty 2004. *Id.* UTC fails to address these factual findings and, as such, it was proper for the court to rely upon UTC's admissions to the FDA regarding the equivalent nature of the Moriarty 2004 and '066 products.[28]

[27] UTC cites no evidence for its argument that "UTC's conversion of treprostinil diethanolamine back into a free acid similarly cannot affect the impurities relevant to the '066 Patent claims." Red Br., 87.

[28] UTC's citation to *Endo Pharmaceuticals Solutions, Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1383 (Fed. Cir. 2018) is inapposite because, as UTC acknowledges, Liquidia never argued that the product-by-process claims are invalid under

The unrebutted evidence of record dictates there is no structural or functional difference between the Moriarty 2004 treprostinil composition and the claimed composition, rendering claims 1-3 and 6 of the '066 patent invalid.

II. The District Court Correctly Found the "Storage at Ambient Temperature" Claim Limitations Not Infringed

The court did not err in concluding Liquidia does not infringe claims 6 and 8 of the '066 patent because TN is never stored at ambient temperature[29] before it is used. Appx00132 (cls. 6, 8).

The focus of a patent infringement inquiry in a Hatch-Waxman case is "what the [NDA] applicant will likely market if its application is approved, an act that has not yet occurred." *Bayer AG v. Elan Pharm. Rsch. Grp.*, 212 F.3d 1241, 1248-49 (Fed. Cir. 2000) (citation omitted). "[T]his hypothetical inquiry is properly grounded in the [NDA] application and the extensive materials typically submitted in its support." *Id.* Following this standard, and considering the evidence of record, the court did not clearly err in concluding that Liquidia's TN is never stored at ambient temperature and is instead stored at 2-8°C. Appx00031-36. UTC attempts to turn this well-settled case law into an allegation that Liquidia, through its NDA

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inherency. *See* Red Br., 88-89. Nor does Liquidia assert an on-sale bar argument. *See id.* at 87 n.12.

[29] The district court construed "ambient temperature" to mean: "room temperature (equal to or less than the range of 15°C to 30°C)." Appx00031.

specification, only "promises that it would not store treprostinil [salt] at ambient temperatures[.]" Red Br., 60-63. Liquidia's non-infringement is based on facts, not promises.

A. TN is Never Stored at Ambient Temperature

Liquidia's NDA includes a Raw Material Specification ("RMS") for TN, which explicitly requires: "Storage Conditions: 2°-8°C, protected from light and moisture." Appx07590; Appx12409; Appx12411. Because this is an NDA requirement, it must be followed and was confirmed during an FDA site inspection documenting that TN is stored in a monitored refrigerator kept at 2-8°C. Appx13102-13103 (310:1-312:1); Appx29531. The RMS is not a "promise" but a regulated requirement—one that UTC disregards because it proves Liquidia does not infringe claims 6 or 8.

UTC instead points to the Drug Master File (DMF) (DMF No. 27680) of Yonsung, the company that makes TN for Liquidia. Yonsung's DMF specifies the storage conditions for TN: "STORAGE: Should be kept in a tight container, protected from moisture and light and stored at 2°C to 8°C." Appx14736; *see also* Appx14207. UTC contends this is only a recommendation, not a requirement, but overlooks the plethora of data the district court relied on proving it is actually followed. Red Br., 63. As the court found, Yonsung's label, certificates of analysis, batch production records, and List of Finished and Intermediate Products dating back

to 2017 require TN to be stored at "refrigerate[d]"[30] temperatures after production is complete and during shipment to Liquidia, which is, and will be, monitored with temperature loggers. Appx00031-32; Appx29572, Appx29583 (Step H5: "refrigerated"); Appx13135-13136 (441:5-445:23); Appx28385; Appx13060 (143:13-144:54). These documents establish Yonsung stores TN at non-ambient temperatures of 2-8°C. *Id.* Further, LGM, an intermediary between Yonsung and Liquidia, also follows the storage conditions set by Yonsung. Appx00031-32; Appx13116-13117 (364:4-10, 367:5-368:7, 370:17-20). Not only does the DMF establish TN ***is not*** stored at ambient temperature, but the court also credited the testimony of Mr. Fuson, Liquidia's FDA expert, who testified that the FDA would expect Liquidia to follow the temperature storage conditions in the RMS as well as Yonsung's DMF. Appx00032; Appx13118 (374:12-15); Appx13124 (396:7-10). This testimony stands unrebutted.

UTC tries to rely on stability data in Liquidia's NDA to suggest that TN is "stable" at ambient temperature, thereby permitting Liquidia to store it as such. Red Br., 62 (citing Appx13596, Appx13802, Appx14209, Appx14211, Appx14219, Appx14207, Appx14739-14772). But UTC's expert, Dr. Nuckolls, admitted that the '066 Patent claims require "actual" storage at ambient temperature, not that TN is

[30] A POSA would understand "refrigerated" to mean within the range of 2-8°C and not ambient. Appx13135 (442:17-21).

simply "capable" of being stored at that temperature. Appx13058-13059 (136:23-137:5)*; Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1329 (Fed. Cir. 2010) ("[I]t is not enough to simply show that a product is capable of infringement; the patent owner must show evidence of specific instances of direct infringement."). Further, both FDA experts, Mr. Fuson (Liquidia) and Mr. Matto (UTC), agreed that if TN was exposed to ambient temperature, despite this stability data, a full investigation would be required. Appx00032 (citing Appx13092-13093 (272:9-274:3); Appx13119 (378:1-15)). Based on this evidence, the court's rejection of UTC's argument was not clearly erroneous. Appx00032-33.

UTC also claims Liquidia made its LIQ861 bulk powder using batches of TN stored at ambient temperature. Red Br., 60, 63. UTC points to TN batches TN116J010, TN117K010, and TN117I010 used to make clinical trial batches ultimately relied on in Liquidia's NDA, and alleges that these batches experienced ambient temperature when being shipped from Yonsung. Red Br., 62-63 (citing Appx13049 (98:14-99:15), Appx13677, Appx14212, Appx14888-14889, Appx14920-14921). The evidence shows, through temperature log data, that TN was stored below ambient temperature during shipping and only spiked from refrigerated to ambient temperature on December 11, 2017. *See* Appx14888-14889; Appx14920-14921. As Liquidia's witness Mr. Kindig testified, December 11, 2017 was the date the shipment was received by Liquidia and the box containing TN was

opened, reflecting a temperature spike when the data logger was exposed to ambient temperature while the TN was unpackaged and refrigerated.[31] *See* Appx14877; Appx14908; Appx14888-14889; Appx14920-14921; Appx13102 (310:1-19); Appx13105-13107 (321:18-328:10).

UTC cites TN batches TN120C010, TN120G010, and TN120I010 that experienced temperature excursions above 8°C during shipping from South Korea. Red Br., 64. UTC asserts that Liquidia accepted those out-of-specification batches, but critically, UTC does not, and cannot, offer evidence that those batches were ever used—a requirement of claims 6 and 8. *Id.* Liquidia's witnesses testified that these batches were placed in quarantine and ultimately restricted to research and development use only and not used to make a pharmaceutical composition/product because of the temperature excursion. Appx30939-30941; Appx13103-13105 (312:2-313:25, 317:1-321:17); Appx13041-13042 (68:12-70:2); Appx13136 (446:1-23). UTC alleges that "[o]nly *after* Liquidia was sued and its witness responsible for analytical testing was deposed about those batches did Liquidia assert that they would not be used to make a pharmaceutical product that would be

[31] UTC also alludes to several batches that were shipped in temperatures below 2°C. Red Br., 63. The infringement inquiry here is governed by whether TN was, or will be, "stored at ambient temperature." Appx00132. Temperatures below 2°C are not "ambient temperature" and thus irrelevant. Nonetheless, Yonsung has certified to the quality of TN stored below 2°C, which permits Liquidia to use it. Appx14173; Appx13081 (226:3-25); Appx13106 (323:8-20); Appx13120 (380:4-22); Appx13136-13137 (446:24-447:7).

marketed for sale[.]" Red Br., 64. Not so. These batches were placed into quarantine upon arrival and never released for GMP purposes per protocol, which pre-dates the filing of the district court action. Appx13080 (223:12-224:13); Appx13081 (226:15-227:6); Appx13103-13104 (312:2-316:16); Appx13112 (348:15-23 (testifying that the out-of-specification batches were quarantined and not allowed for GMP use); Appx29349-29373 (Standard Operating Procedure on the Receipt, Handling, and Control of Materials dated October 6, 2019).

Finally, UTC cites to batches that did not include temperature logger data in an attempt to shift its own burden to prove infringement into Liquidia's burden to prove non-infringement. Red Br., 64-65. It is the "[t]he patent owner [that] has the burden of proving infringement and must meet its burden by a preponderance of the evidence." *Takeda Pharm. Co. v. Teva Pharms. USA, Inc.*, 668 F. Supp. 2d 614, 619 (D. Del. 2009). The absence of a temperature logger does not establish the court's opinion was clearly erroneous, particularly given, as discussed above, the extensive documentation requiring TN to be stored at 2-8°C. *See Brigham & Women's Hosp., Inc. v. Perrigo Co.*, 761 F. App'x 995, 1003-04 (Fed. Cir. 2019) ("speculative data … cannot sustain [patentee's] burden of proof.").

UTC's reliance on *Sunovion Pharms., Inv. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271, 1280 (Fed. Cir 2013) is misplaced. Red Br., 61. In *Sunovion*, the claim limitation was "less than 0.25%" and the ANDA recited "[not more than] 0.6%."

731 F.3d at 1274-75. The "[not more than] 0.6%" range ***was*** within the scope of the patent and thus Teva infringed. *Id.* at 1280. Here, storage of TN prior to its use is not "within the scope of a valid patent," but instead is outside the claimed ambient temperature range of "room temperature (equal to or less than the range of 15°C to 30°C)." That is, unlike *Sunovion*, the temperature ranges do not overlap and, as such, Liquidia does not infringe claims 6 or 8, and the court's decision should be affirmed.

B. Yonsung's DMF and Liquidia's NDA Are Regulatory Requirements, Not Merely Promises

UTC contends that the court "faulted" UTC for not proving "*actual past infringement*." Red Br., 66. The court made no such requirement and, in fact, confirmed during trial and in its decision that the infringement inquiry is determined based on what Liquidia will do in the future if LIQ861 is approved. Appx13251 (901:6-11); Appx00022.

UTC asserts that Liquidia has only "pledged" not to infringe. Red Br., 67-68. But UTC points to no document reflecting a mere "pledge." Liquidia is compelled, not merely encouraged, by federal regulation to adhere to the 2-8°C storage requirement in its NDA. 21 C.F.R. §211.80, titled "Current Good Manufacturing Practice for Finished Pharmaceuticals," provides that "[t]here shall be written procedures describing in sufficient detail the … storage … of components and drug product containers" and that "such written procedures shall be followed." 21 C.F.R.

§211.80; *see also* Appx13118-13119 (374:3-377:14); *Abbott Lab'ys v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002) ("Because drug manufactures are bound by strict statutory provisions to sell only those products that comport with the []NDA's description of the drug, an []NDA specification defining a proposed [product] in a manner that directly addresses the issue of infringement will control the infringement inquiry."); *In re Brimonidine Pat. Litig.*, 643 F.3d 1366, 1378 (Fed. Cir. 2011) ("We cannot assume that [the NDA filer] will not act in full compliance with its representations to the FDA[.]"). Because Liquidia's NDA and Yonsung's DMF require storage at 2-8°C, these documents "directly address" the infringement inquiry and control.[32] *See Par Pharm., Inc. v. Hospira, Inc.*, 835 F. App'x 578, 586 (Fed. Cir. 2020) ("[R]epresentations about the []NDA's scope control the infringement analysis"); Appx13118-13119 (374:3-377:14 (discussing 21 C.F.R. §211.80)); Appx13124 (396:7-10); Appx29531.

The evidence also establishes that it is in Liquidia's interest to not treat the storage conditions as "optional," because "being outside of the temperature range represents a quality of risk that [Liquidia is] not willing to take." Appx13103

[32] UTC assertion that "[n]othing in Liquidia's NDA *requires* Liquidia to store treprostinil salt in refrigerated conditions[,]" is incorrect. Red Br., 68. Liquidia's RMS for TN explicitly requires: "Storage Conditions: 2°-8°C, protected from light and moisture," which must be followed and was specifically checked by the FDA during an on-site inspection. Appx07590; Appx29531.

(311:12-312:1, 314:1-25); Appx13041-13042 (67:19-69:2). When POSAs receive chemical material with specified storage conditions, they consider the conditions as a mandate, not an option—a POSA "would risk compromising the material" otherwise. Appx13134 (435:10-22); *see also* Appx13121 (386:2-8), Appx13124 (396:2-10). Even UTC shipped TN in cold-pack conditions to its expert Dr. Smyth, who then stored the TN at refrigerated conditions because it was shipped cold. Appx13245-13246 (879:15-880:18 (Smyth)); Appx29823-29851; Appx13135 (440:3-441:4).

C. The District Court Did Not Err in its Construction of "Storage"

UTC is incorrect that the court determined "'storage' during the shipment process is still storage, but 'storage' during a later phase of the manufacturing process cannot be." Red Br., 68-69. UTC's error stems from its mischaracterization of Liquidia's PRINT process, which the court correctly found constitutes "use," not storage, of TN. Appx00035-36.

Part of Step 1 of Liquidia's PRINT process—"***Preparation*** of aqueous stock solution"—involves placing TN in a dry box to remove a sample. Appx14132; Appx13039 (59:15-60:18); Appx13061 (146:20-22); Appx13137 (447:20-448:23). The court ***disagreed*** with UTC's expert's testimony that the dry box step was

storage, finding instead that during Step 1, TN is being "used" not "stored."[33] Appx00036 (citing Appx14131 (calling the PRINT process a "manufacturing process")). Each procedure in Step 1 of the PRINT process describes active ***use*** of TN—*e.g.*, "[c]omponents are combined," "components are stirred to dissolve," "[s]olution is filtered[.]" Appx14133. Rather than taking an inconsistent position, as UTC suggests, the court instead determined that the plain and ordinary meaning of "storage" cannot encompass "use" of TN during the PRINT process. It would betray the plain and ordinary meaning of "storage" to hold that the term encompasses active process steps. *See* Appx13137-13138 (450:16-454:20).

UTC's cases are inapposite. Red Br., 70. *Intervet* and *Vita-Mix* both reversed summary judgments of noninfringement based on claim constructions later in the case that were inconsistent with the district courts' earlier claim constructions of those same terms. *See Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1289-1290 (Fed. Cir. 2010); *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1323-24 (Fed. Cir. 2009). Here, the court construed "storage" to have its plain and ordinary meaning (Appx04889) and applied that same meaning in its decision. Appx00031. Thus, the district court did not apply inconsistent constructions for the term "storage."

[33] UTC contends that TN is stored for 3 hours in a dry box, but the cited document does not support that conclusion. Red Br., 69; Appx13924 (no time specified in Step 2-3, where TN is placed in the dry box).

UTC has failed to establish the court's noninfringement findings with respect to claims 6 and 8 were clearly erroneous, and thus its decision should be affirmed.

D. Claim 8 is Not Infringed Because Ambient Storage Does Not Occur Between PRINT Process Steps 1-4

UTC alleges that the court's non-infringement finding for claim 8 is based on an erroneous "construction." Red Br., 71. Attempting to turn this into a *de novo* review of a claim construction ruling, UTC admits that its problem with the court's decision is not its construction of the claims, but "construction of when Liquidia begins preparing the 'pharmaceutical composition'[.]" *Id.* Thus, this is not a claim construction issue, but an issue of the court's factual findings concerning Liquidia's PRINT process reviewed for clear error.

UTC argues that Liquidia infringes claim 8 of the '066 patent because (1) preparation of the "pharmaceutical product" of claim 8 begins at Step 5 of the PRINT process and (2) ambient storage of TN occurs during Steps 1-4 of the PRINT process. Red Br., 72-73. UTC fails to prove both of these theories.

First, preparation of the final LIQ861 product (the accused "pharmaceutical product") does not begin with Step 5 but with Step 1 of the PRINT process. Appx00037. Experts from both parties agreed that a POSA would understand the process of "preparing a pharmaceutical product" in claim 8 begins when the TN is dissolved in water and mixed with excipients in Step 1. Appx13137-13139 (448:11-449:9, 452:24-455:18); Appx13064 (147:3-18 (agreeing that once TN is put in

solution in Step 1, Liquidia is "in the process … of making the pharmaceutical product" of claim 8)). Steps 5 and 6 of the PRINT process—named "Drug Product Primary Packaging" and "Drug Product Secondary Packaging" respectively—simply involve encapsulating and packaging the LIQ861 bulk powder produced in Step 4. Appx14132; Appx13139 (455:9-12). That LIQ861 bulk powder is stored at 2-8°C[34] at the end of Step 4, does not mean that the PRINT process artificially delineates between preparing a "pharmaceutical composition" and "preparing a pharmaceutical product," as UTC contends. Red Br., 74; Appx14136; Appx14142 ("Bulk LIQ861 inhalation powder is stored in the pouch for NMT 6 months at 2°C to 8°C[.]"); Appx13062 (149:9-150:16). The PRINT process is a single manufacturing process, not two. Appx14132 (listing all six steps as one process). Further, the district court found, crediting Dr. Winkler as opposed to Dr. Nuckolls, that "a POSA would understand that the encapsulation and packaging performed during [steps 5-6] would not change the chemical properties of the bulk LIQ861" powder produced in Steps 1-4, and thus, the process of "preparing a pharmaceutical product" begins with Step 1 of the PRINT process. Appx00037 (citing Appx13139 (455:5-18)). UTC has identified no clear error in the court's fact finding.

[34] UTC conveniently fails to note the below ambient storage conditions between Steps 4 and 5.

Second, because the process of making the "pharmaceutical product" begins with Step 1, the "hold times" UTC references in Steps 1-4 would not be "storage" because claim 8 requires "storage" ***before*** preparing. Appx00037. A POSA would also understand hold times where the material is continuing to dry and undergoing change is not storage. Appx13138-13139 (454:10-20, 456:15-20). Drying is an active process, not static in nature. *See id.* Further, none of the hold times for Steps 1-3 indicate storage at ambient temperature. Appx29337-29339.

Nonetheless, even if preparing the "pharmaceutical product" were to start with Step 5 of the PRINT process, Liquidia would still not infringe. Step 5 starts with "Bulk LIQ861 Inhalation Powder" as the first input material, not TN, which is required by claim 8.[35] Appx14137, Appx14142. Once TN is dissolved in water in Step 1, it is dissociated into treprostinil and sodium ions in solution and is mixed with other materials (*i.e.*, excipients). Appx13137 (450:1-15); Appx13206 (722:10-19); Appx13211 (741:7-16). Despite having samples of LIQ861 bulk powder to test, UTC offered no evidence that "treprostinil sodium," which is required by claim 8, is present at all in any step of manufacturing following the complete dissolution of TN at Step 1. Appx30890-30891, ¶¶53-55.

[35] In arguing for the validity of claims 1-3 and 6, UTC seemingly admits the LIQ861 bulk powder does not contain treprostinil sodium, when referencing "comparisons between treprostinil salt and a final treprostinil product[.]" Red Br., 86.

Finally, UTC attempts to manufacture a distinction where "the 'pharmaceutical composition' of claims 1-6 is not a ready-for-sale 'product'; in contrast, the 'pharmaceutical product' of claim 8 is the final ready-for-sale product in its final dosage form prepared for patient purchase and consumption[.]" Red Br., 75. UTC cites no evidence supporting this alleged distinction. *Id.* Claim 8 does not require a "ready-for-sale" product, nor does it include any step of combining treprostinil with excipients, encapsulating it, or packaging it into a final dosage form for sale as UTC contends. All that is required is "a pharmaceutical product comprising treprostinil." Appx00132 (cl. 8). The specification makes no distinction between a "pharmaceutical composition" and a "pharmaceutical product," and again includes no description of combining treprostinil with any excipients. Appx00121-00132. The court expressly found that "a POSA reading the '066 patent specification would understand that treprostinil is a "pharmaceutical composition[/product] comprising treprostinil." Appx00040 (brackets in original). UTC is incorrect that the "pharmaceutical product" must be anything more than treprostinil.

The court's finding that Liquidia does not infringe claim 8 was not clearly erroneous and should be affirmed.

CONCLUSION

Liquidia respectfully requests reversal of the court's judgment as to invalidity and liability for induced infringement of the '793 patent, and as to infringement of claims 1-3 of the '066 patent. Additionally, Liquidia respectfully requests affirmance of the court's judgment as to invalidity of claims 1-3 and 6 of the '066 patent, and non-infringement of claims 6 and 8.

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Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

The foregoing filing complies with the type-volume limitations of the Federal Rules of Appellate Procedure and Federal Circuit Rules, has been prepared using a proportionally-spaced typeface, and includes 13,920 words.

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